'Prefrontal' Cognitive Performance of Healthy Subjects Positively Correlates With Cerebral FDOPA Influx: An Exploratory [^{18}F]-fluoro-L-DOPA-PET Investigation

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Abstract: Dopamine neurotransmission influences those cognitive processes, which are generally regarded as prefrontal cortical functions. In previous positron-emission-tomography (PET) studies, net blood-brain clearance of [^{18}F]-fluoro-L-DOPA (FDOPA) correlated with impaired cognitive performance in patients with Parkinson's disease or schizophrenia. We hypothesized that FDOPA influx also correlates with performance of cognitive tasks associated with prefrontal functioning in healthy volunteers. The net blood-brain clearance of FDOPA (K_{in}^{app}) was mapped in a group of 11 healthy volunteers and calculated in striatal volumes-of-interest. The Wisconsin-Card-Sorting-Test (WCST), Stroop-Test, Trail-Making-Test (TMT-A/B), and Continuous-Performance-Test (CPT-M) had been administered previously to the same subjects. No correlation of K_{in}^{app} with perseverative errors in WCST or age could be found. However, there were significant positive correlations between the magnitude of K_{in}^{app} in caudate nucleus, putamen, and midbrain with performance of the TMT-B, CPT-M, and the Stroop test. Highest correlations were found between the time needed to perform the Stroop interference task and the K_{in}^{app} of striatal areas (Caudate nucleus: -0.780, $P = 0.005$; putamen: -0.870, $P < 0.001$). Thus, the present findings reveal a strong correlation between dopamine synthesis capacity in striatum of healthy volunteers and performance of cognitive tasks linked to the prefrontal cortex. *Hum Brain Mapp 28:931–939, 2007.* ©2006 Wiley-Liss, Inc.

Key words: [^{18}F]-fluoro-L-DOPA; dopamine; striatum; attention; interference; set shifting

INTRODUCTION

Mesencephalic dopamine neurons give rise to innervations of telencephalic structures [Dahlstroem and Fuxe, 1964; Stamford et al., 1988] implicated in extrapyramidal motor function, motivation, and cognition. These diverse functions of dopamine innervations have been attributed to segregated pathways involved with sensorimotor, affective, and cognitive functions [Alexander et al., 1986]. In patients with Parkinson's disease, positron-emission-tomography (PET) stud-

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ies of the cerebral utilization of the DOPA decarboxylase substrate [^{18}F]fluoro-l-DOPA (FDOPA) reveal loss of putaminal innervation correlating with severity of motor symptoms [Brooks, 2000; Cumming and Gjedde, 1998]. In other studies, reduced FDOPA influx to frontal cortex has been linked with impaired cognitive function in patients with Parkinson's disease [Nagano-Saito et al., 2004; Rinne et al., 2000]. In most PET studies of patients suffering from schizophrenia, striatal FDOPA utilization is elevated [Hietala et al., 1995; Reith et al., 1994], especially in patients with predominant positive symptoms [Dao-Castellana et al., 1997]. There was a negative correlation between striatal FDOPA uptake and cognitive performance in patients suffering from schizophrenia, but no such correlations in the healthy control group [Meyer-Lindenberg et al., 2002]. Thus, the relationship between FDOPA utilization and cognition is well established in clinical groups. However, little is known about the relationship between FDOPA influx and performance of frontal cognitive function in healthy subjects.

The frontal cortex subserves specific cognitive functions, notably sustained attention, working memory, conflict control, and decision-making. Specific aspects of these functions can be quantified using instruments such as the Munich version of degraded-stimulus continuous performance test (CPT-M), the Wisconsin card sorting test (WCST), the Stroop test, the auditory verbal learning test (AVLT), or the n-back task [Dujardin et al., 2001; Fey, 1951; Orzack and Kornetsky, 1966; Seidel and Joschko, 1990]. We hypothesized that the frontal cortex and the basal ganglia operate as a functional unit in the performance of these cognitive tasks. This scenario predicts that individual performance of cognitive tasks would consequently correlate with utilization of FDOPA in the basal ganglia of healthy volunteers. Furthermore, we predicted that this correlation would be most evident in the caudate nucleus, which is recipient of dense innervations from the frontal cortex and is implicated in cognitive function. To test these hypotheses, we carried out quantitative FDOPA-PET studies in a series of 11 healthy volunteers who had previously been examined with a battery of cognitive tests.

SUBJECTS AND METHODS

The study was approved by the Ethics Committee of the University of Mainz and the German radiation safety authorities in accordance with national and international standards.

Participants

Eleven male subjects gave written, informed consent to participate in the study. All subjects underwent physical and mental-state examinations and were found to be free of any mental disorder. They reported no intake of drugs, in particular centrally acting agents, for at least six weeks. As all of the participants had to be free of any mental illness, no subjects had ever taken antidepressants, antipsychotics, or mood stabilizers. None of the subjects suffered from clinically significant somatic or neurological—in particular extrapyramidal—complaints. The subjects' age ranged from 21 to 64 years (mean ± *SD*: 32 ± 13 years). A T1-weighted 3D gradient echo magnetic resonance scan was performed to check for possible anatomical abnormalities and for anatomical coregistration before PET scanning (vide infra).

Neuropsychological Testing

For determination of higher cognitive functioning (i.e., working memory, sustained attention, cognitive variability) one day prior to scanning, all subjects underwent a neuropsychological testing battery, including the continuous performance test (CPT), the trail-making tests A+B (TMT-A; TMT-B), the WCST, and the Stroop-Test [Baumler, 1985; Heaton et al., 1993; Reitan, 1958; Rosvold et al., 1956].

Continuous performance test

We used the computerized Munich version (CPT-M) of the CPT [Kathmann et al., 1996]. During this test, 480 blurred digits are presented successively on a 15-inch monitor for 42 min. Between every presentation an interstimulus interval of 1 s was interposed. The task was to press a button as fast as possible every time the digit "0" (25% of all stimuli, randomly distributed) was presented. A training phase of 160 presentations preceded the main task. Outcome measures were the mean reaction time, the percentage of correctly identified "0" digits (hits), the nonparametrical sensitivity index ($P(\bar{A})$), and the response criterion ($\ln(\beta)$). $P(\bar{A})$ and $\ln(\beta)$ are parameters according to signal detection theory (SDT), calculated as described previously [Aaronson and Watts, 1987]. The sensitivity indices describe the subject's ability to discriminate target from nontarget stimuli, while the response criterion expresses the amount of evidence the subject requires to decide that a given stimulus is a target.

Stroop test

A German-language pencil-and-paper version [Baumler, 1985] of the original Stroop test [Stroop, 1935] was used. Subjects are successively shown three cards. Card I contains 72 color words printed in black that have to be read by the subject (Read color words; RCW). Card II contains rows of 72 colored boxes, and the subject names the colors (Name colored bars; NCB). Card III contains the same amount of color-words printed in conflicting colors (e.g., "blue" printed in red ink); the subject has to name the color, ignoring the word (Name colored words; NCW). Subjects perform all parts of the task three times. For RCW, NCB, and NCW the time durations were measured, which the subjects needed to perform the task. As outcome parameter the median of the three runs per task were used.

Trail making test A and B

The trail making test parts A + B were recorded on pencil-and-paper. In part A, the sheet consists on 25 consecutively numbered circles spaced around the page. The test subject should connect the circles by one single line in the correct

order. In part B the subject is asked to draw a line alternating between 12 numbered and 12 lettered circles in ascending order. The outcome parameter is the time (in seconds) required to complete each section of the test (in seconds). There was one training session with eight numbered circles and four numbered and four lettered circles before the tasks were performed.

Wisconsin card sorting test

The WCST was administered in a computerized version (WCST Computer Version-2; Psychological Assessment Resources). Briefly, each card shows different symbols (e.g., stars, triangles, crosses, or circles) in varying colors (e.g., red, blue, green) and numbers. The subject is asked to sort these cards to match the reference cards by some criterion. The subject is not cued to sort by a particular criterion, but is informed whether or not the sorting is correct. Once the correct rule has been discovered and 10 consecutive correct sorts are made, the rule is changed without warning. The subject has to discover the new sorting rule. The test ends if six of these blocks are performed or 128 cards have been sorted. As main outcome variables the percentage of total errors and the perseverative errors have been chosen. The data were not corrected for age and education.

PET Data Acquisition

Decarboxylation of FDOPA in peripheral tissues was blocked by oral administration of carbidopa (Merck Sharp kg body weight) 1 h prior to injection of FDOPA. All PET recordings were obtained with the Siemens ECAT EXACT whole-body PET, which has a field-of-view of 16.2 cm in 47 planes, an inter-plane spacing of 3.375 mm and an axial resolution of 5.4 mm FWHM. After a brief attenuation scan, a sequence of 30 emission frames lasting a total of 124 min was recorded. Frame length increased progressively according to the following schedule: 3 × 20 s; 3 × 1 min, 3 × 2 min, 3 × 3 min, 15 × 5 min, and 3 × 10 min [Gründer et al., 2003]. A mean of 195 MBq FDOPA (SD: 34.4 MBq, range: 137–263 MBq) was injected intravenously as a bolus into a cubital vein. During the first 10 min after FDOPA injection, radioactivity concentration in blood from a radial artery was recorded at intervals of 1 s using an on-line γ counter cross-calibrated to the tomograph; thereafter, a series of 15 arterial blood samples were drawn manually according to the following schedule: 2 × 2 min, 2 × 3 min, 2 × 5 min, and 9 × 10 min, and blood radioactivity concentration was measured using well-counter. The fractions of untransformed FDOPA and its major plasma metabolite 3-*O*-methyl-[^{18}F]-fluorodopa (OMFD) were measured by reverse-phase high performance liquid chromatography (HPLC) [Cumming et al., 1993] in plasma samples prepared from arterial blood collected at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min. The continuous input functions of plasma FDOPA and OMFD were calculated by interpolation of biexponential function to the measured fractions [Gillings et al., 2001]. In case of two subjects the HPLC chromatography failed due to technical problems. Thus, the time course of FDOPA and OMFD fractions was nonlinearly fitted using the fraction results of the remaining nine subjects.

PET Data Analysis

The entire dynamic PET sequences, consisting of 30 frames, were realigned and corrected for interframe head-motion using a rigid-body transformation with 6° of freedom, and employing an MRI derived 4D-template specific for FDOPA [Kumakura et al., 2004; Reilhac et al., 2003]. After motion correction, individual summed emission images were calculated. The summed images were registered to the MNI stereotaxic brain, using the affine transformation of the AIR algorithm [Woods et al., 1992] for fitting to a grey matter MRI template of MNI average brain [Collins et al., 1998] with its striatum intensity doubled in order to emulate radioactivity distribution of the summed FDOPA emission images. Parametric maps of the net blood brain clearance of FDOPA (K_{in}^{app}) were obtained by linear graphical analysis of data recorded in the interval 16–54 min, with subtraction of the time-radioactivity curve measured in cerebellum [Martin et al., 1989], and assuming irreversible trapping during the time interval [Kumakura et al., 2005]. Using a ROI-template of bilateral putamen (9.7 cm^3), bilateral caudate nucleus (8.5 cm^3), midbrain (5.9 cm^3), and cerebellum (48.3 cm^3) obverse average ROI-based K_{in}^{app} values were derived [Vernaleken et al., 2006].

Statistical Analyses

Spearman rank correlations were calculated for correlations between cognitive test parameters, age, and the K_{in}^{app} of every volume of interest (VOI). Furthermore, intercorrelations between the cognitive parameters were determined. In all analyses, the two-tailed level of statistical significance was set at $\alpha = 0.05$. Due to the exploratory character of the study and the high intercorrelations between several cognitive test parameters, primarily no adjustment for multiple testing was performed. In a next step a correction according to Bonferroni-Holm [Holm, 1979] was performed (bilateral results included; $k = 33$).

RESULTS

Results of the cognitive tests are shown in Table I. One subject discontinued the WCST; another subject's WCST failed due to technical problems. During the evaluation of TMT-B in one case an initially undetected misconnection became obvious. Individual magnitudes of K_{in}^{app} in VOIs for caudate, putamen, and midbrain are listed in Table II. In this population age was without effect on the magnitudes of striatal and midbrain K_{in}^{app}. There was an age-dependent decline in the response criterion (ln(β)) of CPT-M with increasing age ($r = -795$; $P = 0.003$; Spearman correlation); results of other cognitive tests did not correlate with age

TABLE I. Individual cognitive outcome parameters of Trail Making Test (TMT-A/B), Munich Version of the Continuous Performance Test (CPT-M), Stroop and Wisconsin Card Sorting Test (WCST)

		TMT		CPT-M			Stroop			WCST	
Subject	Age	Part A (s)	Part B (s)	Reaction (ms)	Hits (%)	$P(\bar{A})$	RCW (s)	NCB (s)	NCW (s)	Total errors (%)	Pers. Err. (%)
1	23	30	79	566	19	0.76	30	53	86	16	7
2	29	26	72	536	33	0.78	34	54	85	10	4
3	51	30	69	465	79	0.93	38	51	80	—	—
4	29	22	68	549	42	0.82	21	34	60	13	7
5	36	26	61	330	27	0.63	32	43	70	35	15
6	23	18	32	582	60	0.89	23	32	44	—	—
7	26	28	66	592	25	0.77	31	49	94	25	10
8	64	31	106	993	6	0.59	64	73	134	47	28
9	24	38	75	522	29	0.81	34	48	85	33	20
10	21	25	—	565	32	0.83	36	58	103	22	9
11	27	23	62	573	63	0.91	33	42	69	48	32

$P(\bar{A})$, nonparametrical sensitivity index; ln(β), response criterion; RCW, read colour words; NCB, name coloured bars; NCW, name coloured words; Pers. Err., perseverative errors.

(Table III), nor did the magnitude of K_{in}^{app} in any brain region. There were no significant side-to-side differences in K_{in}^{app} for any striatal VOI. Nonparametric correlation analysis of the K_{in}^{app} results in the subcortical structures with neuropsychological test performance yielded significant positive correlations with the CPT hit score as well as with sensitivity indices, and negative correlations with time durations to process the TMT-B and Stroop interference tasks (NCB/NCW) (Table III and Fig. 1). After Bonferroni-Holm correction correlation between the NCB and NCW time scores and the net blood brain FDOPA uptake in putamen remained still significant.

DISCUSSION

The present study reveals significant correlations between several prefrontal cognitive functions and presynaptic dopamine synthesis capacity in the basal ganglia and cortex, measured as net blood brain clearance of FDOPA (K_{in}^{app}) in a group of 11 healthy volunteers. Although the study followed an exploratory design, a Bonferroni-Holm correction was additionally performed *post hoc*. Even when a Bonferroni-Holm correction was applied, the observed negative correlations between the time needed for the Stroop NCB and NCW tasks and putaminal K_{in}^{app} reached the level of significance. A number of other correlations also reached significance in the single analysis, but failed the Bonferroni-Holm correction. In particular, the magnitude of K_{in}^{app} in putamen correlated significantly with TMT-B results. The magnitude of K_{in}^{app} in the caudate nucleus likewise correlated positively with performance of components of the CPT-M while the magnitude of K_{in}^{app} in midbrain correlated with CPT-M results and Stroop performance. The composite of these cognitive tasks reflects the performance of prefrontal cortical functions, specifically sustained attention, working memory, conflict-control, and stimulus discrimination. Thus, in agreement with our hypothesis, we found FDOPA utilization to be highest in the basal ganglia of healthy subjects with relatively good per-

TABLE II. Individual analysis of net blood brain clearance of FDOPA (K_{in}^{app}; ml g^{-1} min^{-1}) in different volumes of interest (VOI)

	Caudate nucleus			Putamen			
Subject	Bilateral	Left	Right	Bilateral	Left	Right	Midbrain
1	0.0059	0.0058	0.0061	0.0085	0.0084	0.0086	0.0026
2	0.0064	0.0066	0.0062	0.0102	0.0101	0.0103	0.0016
3	0.0084	0.0088	0.0080	0.0126	0.0123	0.0128	0.0030
4	0.0119	0.0134	0.0104	0.0137	0.0136	0.0138	0.0052
5	0.0076	0.0082	0.0070	0.0135	0.0133	0.0136	0.0028
6	0.0071	0.0075	0.0068	0.0146	0.0152	0.0138	0.0052
7	0.0064	0.0067	0.0061	0.0098	0.0096	0.0101	0.0011
8	0.0056	0.0051	0.0061	0.0096	0.0092	0.0099	0.0016
9	0.0079	0.0074	0.0083	0.0135	0.0130	0.0140	0.0049
10	0.0059	0.0056	0.0063	0.0075	0.0078	0.0073	0.0027
11	0.0082	0.0080	0.0084	0.0124	0.0116	0.0132	0.0029
AVE	0.0074	0.0076	0.0072	0.0114	0.0113	0.0116	0.0031
STD	0.0018	0.0022	0.0014	0.0024	0.0024	0.0024	0.0015

TABLE III. Correlation analysis (Spearman Rank Order Correlation, two-tailed) between net blood brain clearance of FDOPA (K_{in}^{app}) in subcortical structures and main cognitive task parameters

	Caudate nucleus			Putamen					
	Bilateral	Left	Right	Bilateral	Left	Right	Midbrain	Age	*n*
TMT									
Part A	*−0.294/n.s.*	*−0.384/n.s.*	*−0.364/n.s.*	*−0.373/n.s.*	*−0.397/n.s.*	*+0.220/n.s.*	*−0.401/n.s.*	*+0.271/n.s.*	*11*
Part B	−0.426/n.s.	−0.612/n.s.	−0.350/n.s.	−0.638/ $P = 0.047$*	−0.673/ $P = 0.033$*	+0.492/n.s.	−0.354/n.s.	+0.189/n.s.	10
CPT-M									
React. time	*−0.525/n.s.*	*−0.518/n.s.*	*−0.505/n.s.*	*−0.346/n.s.*	*−0.355/n.s.*	*−0.374/n.s.*	*−0.352/n.s.*	*−0.205/n.s.*	*11*
ln(β)	*−0.046/n.s.*	*−0.200/n.s.*	*+0.083/n.s.*	*−0.241/n.s.*	*−0.273/n.s.*	*−0.118/n.s.*	*+0.046/n.s.*	*−0.795/ $P = 0.003$***	*11*
Correct hits	+0.731/ $P = 0.011$*	+0.664/ $P = 0.026$*	+0.706/ $P = 0.015$*	+0.515/n.s.	+0.509/n.s.	−0.442/n.s.	+0.644/ $P = 0.033$*	+0.018/n.s.	11
P($\bar{A}$)	+0.603/ $P = 0.050$*	+0.491/n.s.	+0.615/ $P = 0.044$*	+0.328/n.s.	+0.309/n.s.	−0.292/n.s.	+0.612/ $P = 0.044$*	−0.228/n.s.	11
Stroop									
RCW	*−0.286/n.s.*	*−0.410/n.s.*	*−0.179/n.s.*	*−0.459/n.s.*	*−0.469/n.s.*	*−0.379/n.s.*	*−0.346/n.s.*	*+0.378/n.s.*	*11*
NCB	−0.726/ $P = 0.011$*	−0.782/ $P = 0.004$**	−0.670/ $P = 0.024$*	−0.852/ $P = 0.001$**	−0.855/ $P = 0.001$**	−0.815/ $P = 0.002$**	−0.735 / $P = 0.010$*	+0.128/n.s.	11
NCW	−0.780/ $P = 0.005$**	−0.838/ $P = 0.001$**	−0.731/ $P = 0.011$*	−0.870/ $P = 0.001$**	−0.879/ $P < 0.001$***	−0.781/ $P = 0.005$**	−0.789/ $P = 0.004$**	−0.034/n.s.	11
WCST									
Total errors	+0.250/n.s.	+0.033/n.s.	+0.085/n.s.	+0.059/n.s.	+0.067/n.s.	+0.117/n.s.	+0.092/n.s.	+0.259/n.s.	9
Pers. Errors	+0.097/n.s.	+0.050/n.s.	+0.162/n.s.	+0.118/n.s.	+0.109/n.s.	+0.201/n.s.	+0.168/n.s.	+0.214/n.s.	9

Parameters not expected to depict prefrontal cognitive functions are presented in italics CPT-M, Munich version of the Continuous Performance Test (ln(β), response criterion; $P(\bar{A})$, nonparametrical sensitivity index).

Stroop Test: RCW, time to "read color word," NCB, time to "name colored bars," NCW, time to "name coloured word."WCST: Wisconsin Card Sorting Test.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

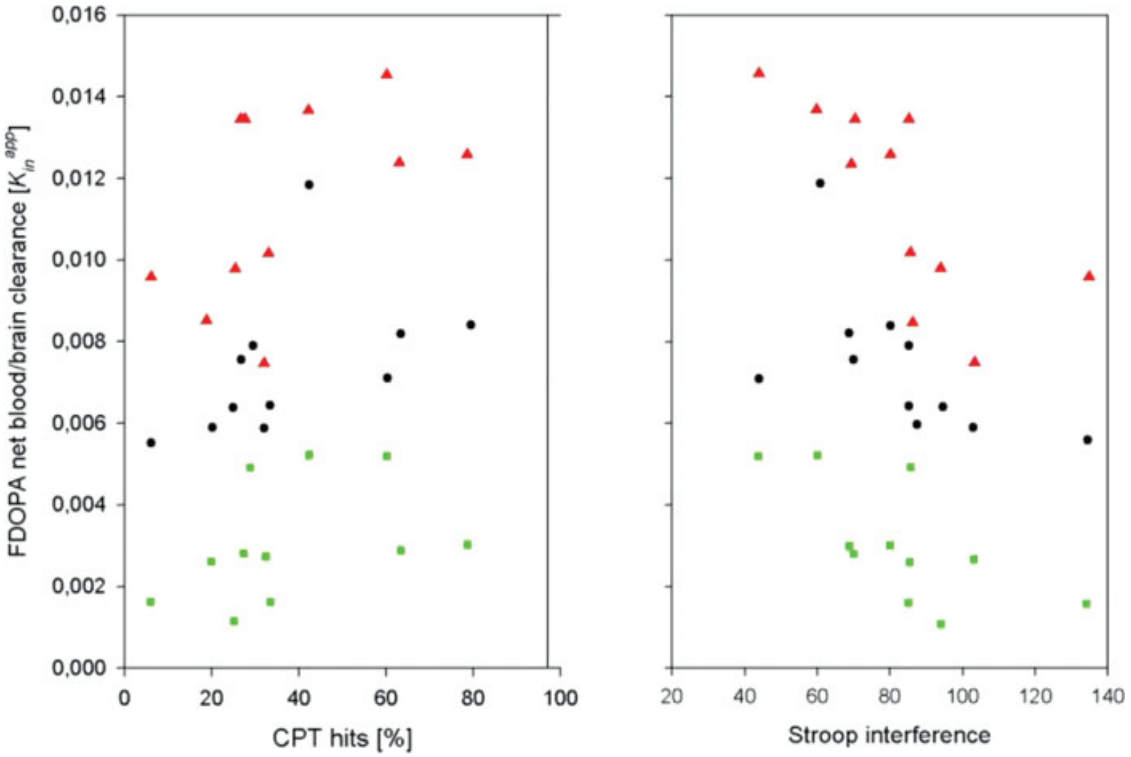

Figure 1.

Scatter plots showing the relation between the net blood/brain clearance of FDOPA (K_{in}^{app}) and neuropsychological parameters. The left plot illustrates the CPT results [% correct hits]; Stroop performance is depicted in the right plot (Interference score [sec]). K_{in}^{app} was calculated for bilateral putamen (red triangles), bilateral caudate nucleus (black circles), and midbrain (blue squares).

formance of these frontal cortical tasks, thus linking subcortical dopamine with cortical function. Only two of eleven significant correlations (bilateral VOIs) between 'prefrontal' cognitive parameters survived the Bonferroni-Holm correction, most likely due to the low subject number. However, all significant correlations uniquely depict higher 'prefrontal' cognitive performance in subjects with relatively higher K_{in}^{app} in striatum or midbrain. Neither inverse correlations between K_{in}^{app} and 'prefrontal' cognitive parameters nor correlations between K_{in}^{app} and secondary parameters such as psychomotor speed could be detected. Nevertheless, the TMT-B results and CPT-M results should be interpreted with caution, due to the exploratory nature of this study in a small group of subjects.

Present estimates of the magnitude of K_{in}^{app} are within the range of earlier reports. We did not find any decline in FDOPA utilization in the basal ganglia as a function of normal aging, in agreement with a number of earlier studies in humans [Cumming and Gjedde, 1998; Doudet et al., 2006; Kumakura et al., 2005] and rhesus monkeys. The only cognitive parameter declining with age in the present group was the response criterion ln(β) in the CPT-M. This decline suggests a more liberal decision-making with increasing age as reported previously by Flicker et al. [1989]. The remaining cognitive parameters showed no significant correlation with age. Thus, age appears not to be a substantial covariat for the correlation in this investigation.

Contrary to part of our hypothesis, correlations between some cognitive scores and the magnitude of K_{in}^{app} were slightly higher in putamen VOIs than in the caudate nucleus and midbrain areas. This finding may reflect the superior stability of K_{in}^{app} estimates in the putamen [Kumakura et al., 2005]; the caudate nucleus is less compact in form than is the putamen, contributing to more pronounced partial volume effects, higher vulnerability to misalignment, and worse accuracy of spatial normalization. The present midbrain VOI is intended to comprise the much smaller substantia nigra and VTA. Thus, it is not surprising that correlations between cognitive scores and K_{in}^{app} in the midbrain tended to be lower than in striatum. Nonetheless, significant correlations were present between CPT-M results (percent correct hits and sensitivity index), Stroop scores (NCB and NCW), and the magnitude of K_{in}^{app} in midbrain, further supporting our claim of an intrinsic interaction between dopaminergic innervations and cognitive performance. Needless to say, the present correlation analysis does not indicate causality; it remains uncertain if higher FDOPA utilization in the striatum facilitates frontal cortical function, or vice versa. Likewise, the earlier

finding of correlations between cognitive functions in schizophrenia and FDOPA influx does not imply a unique causal process [Meyer-Lindenberg et al., 2002].

In the present study, no analysis in respect to the magnitude of K_{in}^{app} in the prefrontal cortex (PFC) was performed; attempts to quantify the cortical FDOPA utilization resulted in very low and unstable estimates of FDOPA influx in that regions due to the low specific signal.

In the present study, a battery of neuropsychological tasks was designed to selectively target attention, working memory, conflict control and stimulus discrimination, all of which are in general considered to be, in the main, frontal lobe functions. The CPT in the present Munich version (CPT-M) can assess parameters for psychomotor processing speed (reaction time), visual vigilance, and sustained attention, and also, on the basis of SDT [Kathmann et al., 1996], is able to distinguish between discriminating ability ($P(\bar{A})$) and the extent of conservative/liberal decision making ($\ln(\beta)$). We found a significant correlation between FDOPA K_{in}^{app} primarily in caudate nucleus and parameters depicting stimulus discriminating ability. In the case of TMT, Part A results are more affected by sensomotor speed whereas the Part B depicts cognitive flexibility and working memory [Kortte et al., 2002]. Thus, only Part B correlates with K_{in}^{app} of striatum. Because the cognitive parameters most sensitive for sensomotor speed, especially TMT-A duration, Stroop RCW results or reaction time in CPT-M, failed to show significant correlation with FDOPA utilization, we conclude that our main findings do not indicate individual sensomotor function *per se*.

Previous human PET-studies focussing on correlations between dopamine neurotransmission and neuropsychology were primarily performed in states of illness. For example, Meyer-Lindenberg et al. [2002] found positive correlations between perseverative errors in WCST and striatal K_{in}^{app} in patients with schizophrenia, but no such correlations in healthy volunteers. Likewise, the magnitude of K_{in}^{app} in striatum did neither correlate with WCST perseverative errors nor with total errors in the present study of normal subjects. Although the missing correlations with WCST results are in agreement with the data of Meyer-Lindenberg [2002] this is not congruent to our results regarding Stroop, TMT-B, and CPT-M tasks. The loss of two subjects while perfoming the WCST cannot fully account for the lack of correlation. Keeping in mind the individual task results, the overall high performance of the subjects becomes apparent. Only two subjects made more than 20% of perseverative errors. We suggest a ceiling effect as the main reason. This hypothesis may be supported by previous investigations comparing patients suffering from schizotypal disorder with healthy controls. The majority of cognitive tasks (including Stroop interference and TMT-B) showed significant differences whereas WCST results did not [Battaglia et al., 1994; Laurent et al., 2000; Mitropoulou et al., 2005].

In an earlier investigation, reduced FDOPA uptake in caudate nucleus correlated with impairments in attention and working memory in patients with Parkinson's disease [Rinne et al., 2000]. In a number of previous PET studies, indicators of dopamine systems have been correlated with behavioural parameters in healthy populations. Suhara et al. [2001] found negative correlations between dopamine D_2 receptor binding in right insular cortex and the novelty seeking trait. In another earlier FDOPA-PET study there was no correlation between K_{in}^{app} and novelty seeking, but there was a negative correlation with anxiety-related personality traits [Laakso et al., 2003]. In a SPECT study, Mozley et al. [2001] found higher dopamine transporter binding in younger subjects with higher levels of neuropsychological performance. Analogously, Volkow et al. [1998] found that age and cognitive task performance correlated negatively with dopamine D_2 receptor availability in striatum. In the only previous FDOPA-PET study of cognition in normal subjects, McGowan et al. [2004] reported greater FDOPA influx in ventral striatum of subjects with higher verbal fluency, whereas the opposite correlation prevailed in patients suffering from schizophrenia. Thus, our finding adds support to the previous literature linking normal cognition and the striatal dopamine innervation, placing emphasis on the frontal tasks of sustained and divided attention, working memory, and conflict control.

A large body of evidence obtained in experimental animals supports a role for dopamine transmission in cognition. For example, dopamine depletion caused initial deficits in spatial memory task in monkeys, which was resolved upon dopamine agonist treatment [Brozoski et al., 1979]. D_1-agonists improve working memory of monkeys after dopamine depletion [Castner et al., 2000], but higher doses interfered with cognitive performance [Arnsten et al., 1994]. Reviewing these and similar results, Arnsten [1997] hypothesized an "inverted-U" relationship of D_1-receptor activation and prefrontal functioning. Similarly, the dopamine D_2-agonist bromocriptine can improve spatial working memory in normal humans with low performance, but interfere in subjects with high performance [Kimberg et al., 1997; Luciana et al., 1992]. In the present study, the range of K_{in}^{app} in a normal group may have been too small to reveal other than a unidirectional relationship with cognitive performance.

As noted above, Meyer-Lindenberg et al. [2002] found lower WCST performance in those patients suffering from schizophrenia with the highest striatal FDOPA uptake. In the same study, during performance of the WCST, the BOLD signal in dorsolateral prefrontal cortex (dlPFC) correlated negatively with K_{in}^{app} in the patients. These authors discuss the results on the base of several direct and indirect projections from cortex to the brainstem. In particular, they mention the possibility of a disinhibition of striatal dopaminergic transmission due to a pathological decrease of prefrontal activity mediated by feedback projections. In the present study of normal controls, we found instead positive correlations between cognitive performance and striatal FDOPA utilization in normal subjects. Congruently, in a [^{11}C]FLB 457-PET activation study, Aalto et al. [2005] found decreased dopamine receptor availability in PFC and anterior cingulate cortex during performance of a 2-back working memory task, link-

ing dopamine release with frontal cortex function during cognition in normal subjects. Although we failed to measure directly the FDOPA influx in dlPFC, the present correlations between cognition and K_{in}^{aPP} in mesencephalon, the site of dopamine neurons projecting to striatum and cortex, is consistent with coupling between dopamine synthesis capacity and frontal cortical function. In non-human primates, prolonged dopamine depletion in PFC led to higher attentional set shifting performance combined with higher dopamine responses in caudate nucleus [Roberts et al., 1994]. They speculated that increased dopamine in striatum might facilitate cognitive set shifting. Our findings likewise link striatal dopamine transmission with prefrontal cognitive performance. Whereas a reciprocal regulation between prefrontal activity and striatal dopamine transmission as depicted by Meyer-Lindenberg et al. [2002] appears to be a predominant mechanism in cases of schizophrenia, the present results suggest a different influence of striatal dopaminergic transmission on prefrontal cognitive performance in the absence of pathological states.

In conclusion, we have measured cognitive function in 11 healthy male subjects, and subsequently conducted quantitative FDOPA-PET studies. The main findings of this study were positive correlations between performance of the Stroop interference test, the CPT sensitivity index, the number of hits, and the TMT-B performance and the magnitude of FDOPA influx in putamen. Similar correlations were detected in the caudate nucleus and in the midbrain. Overall, these results are consistent with our claim that dopamine synthesis capacity in the basal ganglia of normal brain facilitates performance of cognitive tasks subserved especially by the prefrontal cortex. Whether these correlations are driven as a top-down process is a matter of speculation, pertinent to an understanding of cognitive function in schizophrenia.

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REFERENCES

Aalto S, Bruck A, Laine M, Nagren K, Rinne JO (2005): Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: A positron emission tomography study using the high-affinity dopamine D2 receptor ligand [11C]FLB 457. J Neurosci 25:2471–2477.

Aaronson D, Watts B (1987): Extensions of Grier's computational formulas for A′ and B″ to below-chance performance. Psychol Bull 102:439–442.

Alexander GE, DeLong MR, Strick PL (1986): Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381.

Arnsten AF (1997): Catecholamine regulation of the prefrontal cortex. J Psychopharmacol 11:151–162.

Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS (1994): Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology (Berl) 116:143–151.

Battaglia M, Abbruzzese M, Ferri S, Scarone S, Bellodi L, Smeraldi E (1994): An assessment of the Wisconsin Card Sorting Test as an indicator of liability to schizophrenia. Schizophr Res 14:39–45.

Baumler G (1985): Farbe-Wort-Interferenztest (FWIT) nach J. R. Stroop (Handanweisung). Gottingen, Germany: Verlag fur Psychologie Hogrefe.

Brooks DJ (2000): PET studies and motor complications in Parkinson's disease. Trends Neurosci 23:S101–S108.

Brozoski TJ, Brown RM, Rosvold HE, Goldman PS (1979): Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205:929–932.

Castner SA, Williams GV, Goldman-Rakic PS (2000): Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. Science 287:2020–2022.

Collins , Zijdenbos AP, Evans A (1998): Improved Automatic Gross Cerebral Structure Segmentation. Montreal, Canada.

Cumming P, Gjedde A (1998): Compartmental analysis of dopa decarboxylation in living brain from dynamic positron emission tomograms. Synapse 29:37–61.

Cumming P, Leger GC, Kuwabara H, Gjedde A (1993): Pharmacokinetics of plasma 6-[18F]fluoro-l-3,4-dihydroxyphenylalanine ([18F]Fdopa) in humans. J Cereb Blood Flow Metab 13:668–675.

Dahlstroem A, Fuxe K (1964): Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol Scand 62(Suppl 232):1–55.

Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, Artiges E, Feline A, Syrota A, Martinot JL (1997): Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophr Res 23:167–174.

Doudet DJ, Rosa-Neto P, Munk OL, Ruth TJ, Jivan S, Cumming P (2006): Effect of age on markers for monoaminergic neurons of normal and MPTP-lesioned rhesus monkeys: A multi-tracer PET study. Neuroimage 30:26–35.

Dujardin K, Defebvre L, Grunberg C, Becquet E, Destee A (2001): Memory and executive function in sporadic and familial Parkinson's disease. Brain 124:389–398.

Fey ET (1951): The performance of young schizophrenics and young normals on the Wisconsin Card Sorting Test. J Consult Psychol 15:311–319.

Flicker C, Ferris SH, Crook T, Bartus RT (1989): Age differences in the vulnerability of facial recognition memory to proactive interference. Exp Aging Res 15:189–194.

Gillings NM, Bender D, Falborg L, Marthi K, Munk OL, Cumming P (2001): Kinetics of the metabolism of four PET radioligands in living minipigs. Nucl Med Biol 28:97–104.

Gründer G, Vernaleken I, Müller MJ, Davids E, Heydari N, Buchholz HG, Bartenstein P, Munk OL, Stoeter P, Wong DF, Gjedde A, Cumming P (2003): Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients in vivo. Neuropsychopharmacology 28:787–794.

Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtis G (1993): Wisconsin Card Sorting Test manual (revised and expanded). Odessa, FL: Psychological Assessment Resources.

Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Kirvela O, Ruotsalainen U, Salokangas RKR (1995): Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346: 1130–1131.

Holm S (1979): A simple sequentially rejective multiple test procedure. Scand J Stat 6:65–70.

Kathmann, Wagner M, Satzger W, Engel RR (1996): Vigilanzmessung auf Verhaltensebene: Der continuous performance test—München (CPT-M). In: Moller H-J, Engel RR, Hoff P, editors. Befunderhebung in der Psychiatrie: Lebensqualität, Negativsymptomatik und andere aktuelle Entwicklungen. Wien, Austria: Springer. pp 331–338.

Kimberg DY, D'Esposito M, Farah MJ (1997): Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport 8:3581–3585.

Kortte KB, Horner MD, Windham WK (2002): The trail making test, part B: Cognitive flexibility or ability to maintain set? Appl Neuropsychol 9:106–109.

Kumakura Y, Danielsen EH, Reilhac A, Gjedde A, Cumming P (2004): Levodopa effect on [18F]fluorodopa influx to brain: Normal volunteers and patients with Parkinson's disease. Acta Neurol Scand 110:188–195.

Kumakura Y, Vernaleken I, Gründer G, Bartenstein P, Gjedde A, Cumming P (2005): PET studies of net blood-brain clearance of FDOPA to human brain: Age-dependent decline of [18F]fluorodopamine storage capacity. J Cereb Blood Flow Metab 25:807–819.

Laakso A, Wallius E, Kajander J, Bergman J, Eskola O, Solin O, Ilonen T, Syvalahti E, Hietala J (2003): Personality traits and striatal dopamine synthesis capacity in healthy subjects. Am J Psychiatr 160:904–910.

Laurent A, Biloa-Tang M, Bougerol T, Duly D, Anchisi AM, Bosson JL, Pellat J, d'Amato T, Dalery J (2000): Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. Schizophr Res 46:269–283.

Luciana M, Depue R, Arbisi P, Leon A (1992): Facilitation of working memory in humans by a D2 dopamine receptor agonist. J Cognit Neurosci 4:58–68.

Martin WR, Palmer MR, Patlak CS, Calne DB (1989): Nigrostriatal function in humans studied with positron emission tomography. Ann Neurol 26:535–542.

McGowan S, Lawrence AD, Sales T, Quested D, Grasby P (2004): Presynaptic dopaminergic dysfunction in schizophrenia: A positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatr 61:134–142.

Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF (2002): Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci 5:267–271.

Mitropoulou V, Harvey PD, Zegarelli G, New AS, Silverman JM, Siever LJ (2005): Neuropsychological performance in schizotypal personality disorder: Importance of working memory. Am J Psychiatr 162:1896–1903.

Mozley LH, Gur RC, Mozley PD, Gur RE (2001): Striatal dopamine transporters and cognitive functioning in healthy men and women. Am J Psychiatr 158:1492–1499.

NaganohyphenSaito A, Kato T, Arahata Y, Washimi Y, Nakamura A, Abe Y, Yamada T, Iwai K, Hatano K, Kawasumi Y, Kachi T, Dagher A, Ito K (2004): Cognitive- and motor-related regions in Parkinson's disease: FDOPA and FDG PET studies. Neuroimage 22:553–561.

Orzack MH, Kornetsky C (1966): Attention dysfunction in chronic schizophrenia. Arch Gen Psychiatr 14:323–326.

Reilhac, Sechet S, Boileau I, Gunn R, Evans A (2003): Motion correction for PET ligand imaging. New York, NY.

Reitan RM (1958): Validity of the Trail Making Test as an indication of organic brain damage. Percept Mot Skills 8:271–276.

Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, Bachneff S, Cumming P, Diksic M, Dyve SE (1994): Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc Natl Acad Sci USA 91:11651–11654.

Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, Solin O (2000): Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]Fluorodopa positron emission tomographic study. Arch Neurol 57:470–475.

Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ, Robbins TW (1994): 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: Possible interactions with subcortical dopamine. J Neurosci 14:2531–2544.

Rosvold HE, Mirsky AF, Sarason I, Bransome ED, Beck LH (1956): A continuous performance test of brain damage. J Consult Psychol 20:343–350.

Seidel WT, Joschko M (1990): Evidence of difficulties in sustained attention in children with ADDH. J Abnorm Child Psychol 18:217–229.

Stamford JA, Kruk ZL, Millar J (1988): Stimulated limbic and striatal dopamine release measured by fast cyclic voltammetry: Anatomical, electrochemical and pharmacological characterisation. Brain Res 454:282–288.

Stroop JR (1935): Studies of interference in serial and verbal reactions. J Exp Psychol 18:643–662.

Suhara T, Yasuno F, Sudo Y, Yamamoto M, Inoue M, Okubo Y, Suzuki K (2001): Dopamine D2 receptors in the insular cortex and the personality trait of novelty seeking. Neuroimage 13:891–895.

Vernaleken I, Kumakura Y, Cumming P, Buchholz HG, Siessmeier T, Stoeter P, Muller MJ, Bartenstein P, Grunder G (2006): Modulation of [18F]Fluorodopa (FDOPA) kinetics in the brain of healthy volunteers after acute haloperidol challenge. Neuroimage 30:1332–1339.

Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, Hitzemann R, Smith G, Logan J (1998): Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatr 155: 344–349.

Woods RP, Cherry SR, Mazziotta JC (1992): Rapid automated algorithm for aligning and reslicing PET images. J Comput Assist Tomogr 16:620–633.